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(Article begins on next page)

# Intrathecal administration of nusinersen in adult and adolescent patients with spinal muscular atrophy and scoliosis: Transforaminal versus conventional approach

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Scoliosis in SMA patients makes intrathecal delivery of nusinersen very challenging.

Nusinersen can be delivered via interlaminar or transforaminal lumbar puncture.

CT-guided transforaminal approach is an effective option for nusinersen release.

Careful selection and multidisciplinary team are needed to minimize SAEs.

## Abstract

Spinal deformities and surgical correction of scoliosis can make intrathecal delivery of nusinersen very challenging. We aim to evaluate the feasibility and safety of intrathecal administration of nusinersen either via interlaminar or transforaminal approach in a cohort of adult and adolescent patients with spinal muscular atrophy (SMA). Twelve patients were treated with nusinersen in our center under CT-guidance; after a CT scan of the lumbar column, we identified a safe virtual trajectory for the needle and defined patients to address to the transforaminal approach (seven patients) or the interlaminar approach (five patients). Out of 47 procedures, all injections but one were successful. There was one adverse event (post-lumbar puncture syndrome) in the interlaminar approach group (out of 20 procedures) and four adverse events in TFA group (out of 27 procedures) including one serious adverse event, a subarachnoid hemorrhage that required hospitalization. Transforaminal approach can be considered an effective option for nusinersen administration but potentially associated with serious complications, therefore it should be recommended in very selected patients.

## 1. Introduction

Spinal Muscular Atrophy (SMA) is one of the most common neuromuscular disorders in childhood with an incidence of 1:10,000 [1] and the first genetic cause of infant mortality.

SMA is caused by a homozygous deletion or mutation in the survival motor neuron 1 gene (SMN1) on chromosome 5q13.2, leading to insufficient levels of SMN protein, which is crucial for motor neuron survival [2]. SMN2, a centromeric copy of SMN1, produce a truncated, highly unstable and non-functional variant of the SMN protein (SMN-Δ7).

There is an inverse, although not absolute, correlation between the severity of clinical manifestations and the number of SMN2 gene in SMA patients so that SMN2 copy number is considered the major phenotypic modifier of the disease [3].

SMA is classified into three subtypes, according to the age of onset of symptoms and the motor milestones achievement: the SMA type 1 is the infantile and the most severe form, with onset before 6 months of age, no control of head movements, and death usually occurring within the second year of life; the SMA type 2,

with onset at 6–18 months and the possibility for patients to sit without support but not walking; the SMA type 3, with onset after 18 months of age, and possibility for patients to stand and walk [1].

Regardless of SMA type, typical clinical features include progressive muscle atrophy due to the degeneration of anterior horn cells, early development of joint contractures and scoliosis, and variable bulbar and respiratory weakness [4], [5].

Scoliosis, secondary to progressive axial muscle weakness, has an incidence of 60–90% in patients with SMA type 1 and 2, starting in early childhood and invariably progressing [1], [6], [7], [8].

In adult patients, spinal deformities create mechanical disadvantages, affect posture, limit mobility and activities of daily living, and possibly increase respiratory and feeding problems [4].

Historically, treatment for SMA relied on a multidisciplinary supportive care focused on respiratory, nutritional, physical and orthopedic interventions [9].

Recently, a new disease modifying therapy, an antisense nucleotide, called nusinersen, was proved to be effective in revert the molecular mechanism of SMA, up-regulating the level of functional SMN protein by modifying the function of SMN2.

Two pivotal trials [10], [11] showed its dramatic effect in children with SMA type 1 and 2, and nusinersen was approved by the United States Food and Drug Administration (FDA) in December 2016 and by the European Medicines Agency (EMA) in May 2017 for all types of SMA.

One of the main limitations of the use of nusinersen is the administration route. In fact, because of its inability to cross the blood–brain barrier, its effectiveness is strictly dependent on local administration, and its use in clinical practice is approved only for intrathecal injection. Standard treatment encompass an initial induction phase with the administration of 12 mg (=5 ml) in four loading doses on days 0, 14, 28, and 63 and maintenance therapy at intervals of 4 months.

Conventional posterior interlaminar approach (ILA) for intrathecal administration of the drug can be very challenging, both in adult SMA patients with progressive severe scoliosis that leads to anatomical distortion and in patients who underwent spinal surgery for scoliosis in the past utilizing growing rods or posterior spinal fusion. In these cases, a transforaminal approach may be the only way to administer the drug, and this approach needs a radiologic guide.

The use of a CT-guided technique for nusinersen intrathecal administration helps to expand the administration of the drug in adult SMA patients with severe spine alterations, improving the rate of success and the compliance to the procedure.

The primary aim of this study was to analyze the feasibility and the safety of the CT-guided intrathecal delivery of nusinersen using either a transforaminal or interlaminar approach in a series of genetic confirmed SMA patients with severe scoliosis and/or previous spinal surgery treated at the Neuromuscular Disease Center of the University of Turin, Italy.

## 2. Patients and methods

Twenty patients (19 adult and one adolescent) were eligible to be treated with nusinersen at our Center. Twelve of them (60%) were addressed to intrathecal nusinersen administration under CT guide. Inclusion criteria were: the presence of a history of spinal surgery for scoliosis; or a scoliosis Cobb angle of more than 50° with vertebrae rotation.

The mean age of patients was  $30 \pm 12.5$  years (range 16–55) at the time of treatment, and were all wheelchair bound. Eight of them (66%) were diagnosed with type 2 SMA and four (33%) with type 3 SMA. All patients signed a written informed consent.

Each case underwent a preliminary multidisciplinary evaluation by a neurologist expert in neuromuscular disorders and an interventional neuro-radiologist, guided by a preliminary scan of the lower part of the lumbar column. Patients with previous posterior spinal fusion surgery or a severe vertebral rotation, preventing conventional interlaminar approach, in which a safe trajectory could have been identified, were treated with the transforaminal approach (TFA).

We defined the rate of success of the procedure as the percentage of procedures in which we successfully delivered the drug in the subarachnoid lumbar space.

We recorded any adverse events (AEs) of the procedure including, but not limited to, pain or discomfort during the procedure leading to sedation needing, post-lumbar puncture syndrome, radiculopathy, respiratory disturbance, bleeding, spinal ischemia and puncture of visceral organs. Serious adverse event (SAEs) were defined according to the criteria of the Food and Drug Administration of the United States of America (<http://www.fda.gov>) [12].

The radiation dose of every CT guided injection was calculated for each patient.

### 2.1. Description of the procedure

Each patient was placed in lateral decubitus position (usually having the convex portion of scoliotic curvature upward), with ventilator assistance, if needed.

The subarachnoid space was visualized under CT guidance and a virtual oblique trajectory was traced on the screen in a preliminary phase, with consideration of the length of the needle and the need to avoid visceral organs, using a 18–20 gauge spinal (Spinocan®) or Chiba (Medax®) needle. Thicker needles were needed to reach the target in case of longer trajectory. The exact localization of the needle was then checked with another scan or confirmed by cerebrospinal fluid (CSF) dripping after needle stylet removal; after extraction of about 5 ml of CSF, 12 mg of nusinersen were administrated through the designated lumbar space.

After the procedure, all patients remained in clinostatic position with fully parameters monitored for at least 3h before discharge.

### 3. Results

Six patients completed the four loading doses; in addition, four patients had their first maintenance dose; one patient received the first two injections and one patient had only his first dose; these account for a total of 47 consecutive treatments.

Seven patients (58%) underwent intrathecal administration of the drug by TFA (L3-L4 or L4-L5) and five patients (42%) followed the conventional interlaminar approach (ILA) (in L3-L4 space) (Fig. 1).

Fig 1

Conventional interlaminar and transforaminal approach.

Axial image from lumbar CT shows (A) interlaminar posterior approach in a 19 years old SMA type 2 patient with previous spinal surgery in a right lateral decubitus position; and (B) transforaminal approach in a 19 years old SMA type 2 patient; spinal instrumentations create an artifact and the vertebrae are rotated to the left; the needle (arrow) is inserted along the axis of the intervertebral foramen and advanced into the thecal sac avoiding abdominal organs. Pa: posterior arch of the vertebra Si: spinal instrumentation Vb: vertebra L: left side.

We used a 22 gauge spinal needle for all patients (except for three patients who required a 20 gauge Chiba needle).

No patients required general anesthesia; only one patient required bland sedation on his first injection.

Each procedure was successful except for one, for a rate of success of 97.9% (46 out of 47 procedures), assuring the correct delivery of the drug in eleven out of twelve patients.

Regarding AEs (see Table 1) in the ILA group, one patient (#03) experienced a mild post-lumbar puncture syndrome with positional headache as the main symptom the day after the first procedure, lasting a week and treated with bed rest, oral hydration and general analgesics, for a total of 5% of AEs in this group (one post-lumbar puncture syndrome out of 20 procedures).

Table 1. Features of SMA cohort: type of procedures and adverse events.

ID number (sex)	SMA type	Age at first dose	Type of procedure (ILA/TFA)	Spinal
surgery (Y/N)	Procedures (no.)	AEs		
#01 (F) 2	19 ILA Y	4 none		
#02 (M)3a	43 ILA N	5 none		
#03 (F) 2	29 ILA N	4 1 PLS		
#04 (M)2	31 ILA Y	5 None		
#05 (F) 3a	55 ILA N	2 none		
#06 (F) 3a	41 TFA N	4 none		
#07 (M)2	19 TFA Y	4 1 PLS		
#08 (M)2	19 TFA Y	5 none		
#09 (M)2	40 TFA N	5 2 L5-radiculopathy		
#10 (M)2	19 TFA Y	1 1 subarachnoid hemorrhage		
#11 (M)2	24 TFA Y	4 none		
#12 (M)2	16 TFA Y	4 none		

SMA type, age at first dose administration of nusinersen, type of procedure (interlaminar or transforaminal approach), previous spinal surgery, number of procedures and number and type of adverse events of each patient. ILA: interlaminar approach TFA: transforaminal approach PLS: post-lumbar puncture syndrome.

Regarding AEs in the TFA group, one patient (#07) reported a post-lumbar syndrome and one patient (#09) experienced a L5 sensory radiculopathy after two out of five injections. Finally, one patient (#10) did not complete the therapy schedule because of a subarachnoid hemorrhage with bleeding up to the fourth ventricle, as documented by a head CT), likely due to accidental puncture of a radicular artery, which occurred during his second injection. The patient was hospitalized and completely recovered in about ten days with demonstration of complete reabsorption of the hemorrhage on head CT one month after discharge. In total, we describe a 15% of AEs in TFA patients, including one serious adverse event (one post-lumbar puncture syndrome, two radiculopathy and one subarachnoid bleeding out of 27 procedures).

The mean radiation dose of a CT guided intrathecal injection was 2.15 mSv (range: 2.01-2.96) per patient.

#### 4. Discussion

In this study, we presented the results of the CT-guided intrathecal administration of nusinersen in adult and adolescent SMA patients with severe scoliosis or previous spine fusion surgery, either with conventional interlaminar or transforaminal technique. Considering the issues related to the administration of the drug in this population, we describe a 98% of success rate and only one serious adverse event. This

multidisciplinary approach let us to treat all SMA patients, regardless age, comorbidities and severity of spinal deformities.

While the literature proved a dramatic effect of nusinersen in infantile SMA patients, only few studies focused on the administration route issues in adult patients, and CT- guided transforaminal approach has been poorly investigated so far.

A previous report described the transforaminal approach for intrathecal nusinersen delivery in five adult SMA patients, for a total of 17 doses and reported no major complications [13]. Nascene et al. reported no SAEs in a cohort of seven adult SMA patients, using CT or fluoroscopy guidance [14].

Wuster et al. reported data of transforaminal approach only in one patient, with CSF contamination indicating traumatic puncture [15].

Our experience confirms that the transforaminal approach is effective in selected patients, with spinal surgery or extreme rotation of vertebrae.

Preliminary CT scan, focused on designated lumbar spaces, can help to identify these patients without an excessive radiation dose. The cooperation among an expert team of intervention radiologists and neurologists is crucial for the selection phase of this approach.

In comparison with fluoroscopic procedure, CT guidance is the best option to visualize both abdominal organs, bone structures and needle trajectory. However, CT guidance fails to recognize vascular structure. To be less traumatic in the foraminal region, a coaxial technique could be used, when a transforaminal approach is needed. Two needles are used: an outer thicker (e.g. 18 G) introducer needle reaches the pre-foraminal area and a longer inner (e.g. 25 G) needle enters the foramen and reaches the subarachnoid space. This is in line with previous observations that thinner needle are correlated with less adverse event like post-lumbar puncture syndrome [16].

A higher rate of AEs was observed in TFA group (15%) in comparison to the ILA group (5%). In particular, one SAE occurred in TFA group, a subarachnoid bleeding, which required hospitalization and completely resolved without consequences in one month.

Transforaminal approach for nusinersen administration may be the only therapeutic option for patients with severe scoliosis or spinal instrumentation but is associated with a greater number of complications, even severe one, when compared to traditional techniques. Therefore, it should be carefully recommended only in selected patients after an expert multidisciplinary discussion.

CT-guided techniques, although their invasiveness and radiation exposure risk, enable all patients with SMA to have access to the only approved therapy for this disease. Several other therapeutic options are in development, including strategies with other administration routes than intrathecal delivery, which will lead to alternative options for these patients.

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